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Imidazole containing ligands for the modulation of physical properties of metal complexes upon (de)protonation

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Abstract—The synthetic route towards a novel tetradentate ligand bearing two amido and imidazole rings is reported. This ligand has been designed to study the relationship between the protonic state of the ligand through the imidazole moieties towards the electronic behaviour of metal complexes.

1. Introduction

Out of the 20 natural amino acids, less than half are found to bind metal ions at the active sites of metalloproteins. L-Histidine is among the most widely spread ligand in the coordination spheres of the metal centres through the nitrogen atom of the imidazole ring. An example for such a coordinating mode is found in myoglobin and hemoglobin, where His 93 residue serves as the axial ligand on the proximal side of the haem prosthetic group confering a high spin state to the pentacoordinated ferrous ion in the native deoxy form.[1] However, in the same systems, another histidine residue (His 64) located at the distal site of the haem chromophore, which is not involved in the immediate coordination sphere of the iron centre is thought to play an active role in the regulation of the substrate affinities. In the Cu–Zn superoxide dismutase, the copper ion is coordinated to four imidazole N atoms of histidine residues out of which one is found in a bridging position between the two metal ions.[2] If the copper ion is essential for the superoxide dismustase activity, the roles of the imidazolate bridge and zinc ion remain unclear.[3] While in urease, two histidine residues are being critical for catalysis, His 219 in the role of substrate binding and His 320 acting as a general base.[4] These few examples support the wide variety of role that the histidine residue plays per se at the active sites of metalloenzymes.

Small peptides like Gly-Gly-His (GGH) have been covalently tethered to various binding proteins and in the presence of nickel(II) ions and oxidants, specific DNA cleavage were detected.[5] However, the seminal work of Margerum et al. on the corresponding tripeptide nickel binding domain has shown that in the presence of O_2, the nickel was oxidised to a +3 state and decomposed with a rapid decarboxylation.[6,7] In line with this research, Collins et al. have later developed a series of tetramido ligands capable of stabilising metal complexes in unusual high oxidation states [8,9] While, imidazole containing ligands have also been developed in the coordination chemistry. However, most of the times the imidazole secondary amino group is protected with a methyl group. The reason behind this is that after coordination of the imino nitrogen atom of the imidazole ring, the secondary amino group can also act as a potential ligand upon deprotonation. Hence for non-saturated metal coordination spheres, deprotonation of bound imidazole group leads to the formation of polynuclear intermetallic complexes. We must point out that this unique property of the imidazole ring has been used in the elaboration of a diversity of geometric and electronic structures.[10] On another scientific lead, 'free' imidazole containing ligands have been designed for the study of the influence of the protonic state of the ligand towards the electronic responses of the complexes. In this case, the coordination sphere of the metal ion is saturated in order to prevent any intermolecular reaction.[11]

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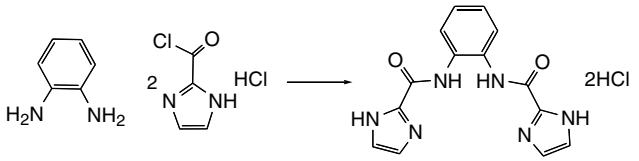


Scheme 1. Synthesis of H_4-L·2HCl.

Benzimidazole ligands have also been prepared with the same goal in mind.[12–14] However, the electronic and structural properties of benzimidazole cannot be related to those of the imidazole ring.[15]

All these challenges have encouraged us to devise the synthesis of a novel family of ligand bearing at the same time two amido groups and two imidazole moieties. Hereby, we describe the synthesis [H_4-L]·2HCl of the acid derivative of the bisamido-bisimidazole ligand. Our first attempt to synthesise the neutral ligand following the procedure by treating the 2-imidazole carboxylic acid derivative with the *o*-phenylene diamine in pyridine and in presence of triphenylphosphite resulted in the formation of a black tar. An elegant alternative to the formation of the amido groups was the use of imidazole acid chloride. This synthetic strategy has been developed by the group of Collman in the preparation of biomimetic models of haem containing enzymes.[16] Treatment of 2 equiv of the 2-chlorocarbonyl imidazole hydrochloride with 1 equiv of *o*-phenylene diamine in the presence of 2 equiv of base, yields after conventional workup the ligand as the imidazolium salt. In our hands, we noticed that upon addition of four equivalents of base in the reacting mixture in order to isolate the neutral form of the ligand resulted in a lower yield (Scheme 1).

The reason behind this, is the probable competition of the nucleophilic attack of the deprotonated imidazolium salt on the acyl chloride with the formation of oligomeric acyl imidazolium species compared to the nucleophilic attack of the amino groups on the acyl chloride.

Crystals of H_4-L were obtained as colourless crystals upon recrystallisation in a mixture of MeOH and alkaline aqueous solution. Figure 1 shows different views of H_4-L. The two amido groups holding the imidazole rings are twisted out the phenyl ring in a disrotatory fashion with a dihedral angle of 46.5° with the phenyl ring.[†]

[†] X-ray data collection for H_4-**L** ($C_{14}N_6O_2H_{12}$), crystal dimensions $0.10 \times 0.08 \times 0.05$ mm, orthorhombic, *Fddd*, $a = 10.3682(11)$, $b = 14.7446(13)$, $c = 37.382(4)$ (Å), $V = 5714.8(10)$ Å, $\rho_{calc} = 1.378$ g cm^{-3}, $T = 100$ K, structure solution with SIR97,[1] refinement against F^2 (SHELXL97[4]) with anisotropic thermal parameters for all non-hydrogen atoms, calculated hydrogen positions with riding isotropic thermal parameters, 10155 data collected, 2572 unique data, 2065 data with $I > 2\sigma(I)$, 100 parameters refined GOF(F^2) = 1.025, final R indices ($R1 = \sum||F_o| - |F_c||/\sum|F_o|$, $wR2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$, $R1 = 0.0433$, $wR2 = 0.1168$, max/min residual electron density 0.475/−0.261 e$^-$Å^{-3}. CCDC 293159.

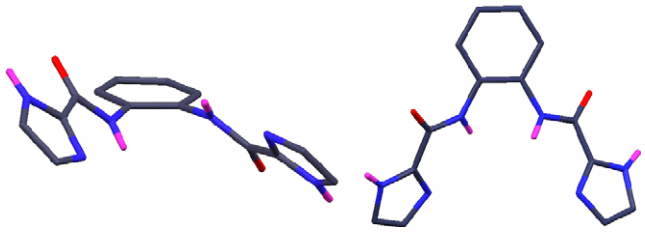


Figure 1. Different views of the molecular unit of H_4-L (only the more acidic protons are shown in pink).

In the crystal lattice two molecular units interlace each other through hydrogen bonding between the NH group of the amido function and the imino nitrogen atoms of the imidazole ring (d H…N = 2.23(8) Å), as depicted in Figure 2. A more complexed hydrogen bonding network runs between the intertwined bimolecular unit through the external O atom of the amido group and the secondary amino group (NH) of the imidazole cycle.

Metallation was carried out after treatment with 4 (i) or 6 (ii) equiv of base followed by addition of Ni(II) salt (Scheme 2) to yield accordingly, the neutral compound [Ni**L**H_2] and the dianionic derivative [Ni**L**]$^{2-}$. The diamagnetic nature of both compounds [Ni**L**H_2] and [Ni**L**]$^{2-}$ was confirmed from their well resolved signals and spectral width of the ^{1}H NMR spectra. This even if the spectra were run in coordinating solvent such as

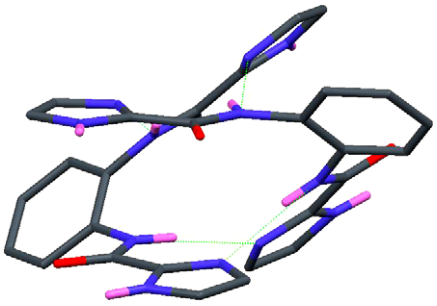
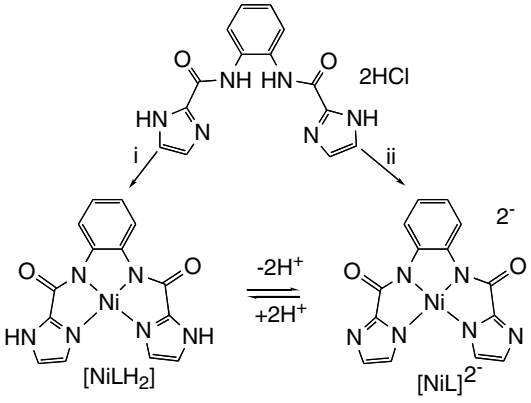


Figure 2. View of the interlacement of two molecular units through hydrogen bonding (only the more acidic protons are shown in pink).



Scheme 2. Synthetic pathway to [Ni**L**H_2] (4 equiv of base+1 equiv of Ni(II) salt) and [Ni**L**]$^{2-}$ (6 equiv of base +1 equiv of Ni(II) salt.

DMSO, thus bringing evidence that no axial coordination occurs at the nickel atom. The presence of the iminic protons of the imidazole groups for $[NiLH_2]$ are detected as a broad signal at around 14 ppm. Upon deprotonation, no signal was detected at low field confirming the loss of the iminic protons. Interestingly, at the same time we noticed an upfield shift of about 0.3 ppm for the aromatic protons at the periphery of the organic skeleton, supporting the fact that there is an increase and a reshuffling of the electronic densities upon the protons abstraction and coordination of the Ni centre (Fig. 3).

The IR spectroscopy also confirms the loss of the iminic protons with the fading of the wide fine structured band in the region ranging from 3130 to 2430 cm^{-1} corresponding to the presence of hydrogen bonding in the solid state. More importantly, a noticeable shift to higher frequencies is observed for the C=O stretching modes on going from $[NiLH_2]$ to $[NiL]^{2-}$. This reflects that in $[NiL]^{2-}$ there is an increase in the transfer of electron density from the deprotonated amido nitrogen atom into the NCO fragment as a consequence of the higher charge relief from the imidazolate groups to the metal centre. This double deprotonation process also affects the electronic absorption spectrum. In the UV region, the intense intraligand charge transfer bands are modified both in intensity and energy. Another salient feature is the shift of the d–d transitions located at the foot of charge transfer transitions at around 430 nm for $[NiLH_2]$ are shifted to higher energies indicating therefore an increase in the ligand field strength perceived by the nickel(II) ion upon deprotonation.

The cyclic voltammograms of $[NiLH_2]$ and $[NiL]^{2-}$ run in DMSO show a remarkable downshift of about 700 mV for the first redox wave. This result indicates that the increase in negative charge on the ligand skeleton shifts the redox potential to less positive values with an average of 350 mV per proton. The magnitude of this shift falls within the same range than that observed for the imidazole containing ligands[11] but nevertheless more important than those for benzimidazole containing ligands (170 mV). [15] EPR spectrum recorded on the monoxidised species of $[NiL]^{2-}$ (after bulk electrolysis at 0.25 V vs SCE) indicates the presence of a nickel(III) complex with a rhombic g anisotropy ($g_x = 2.08$, $g_y = 2.02$ and $g_z = 2.00$, see Supplementary data).

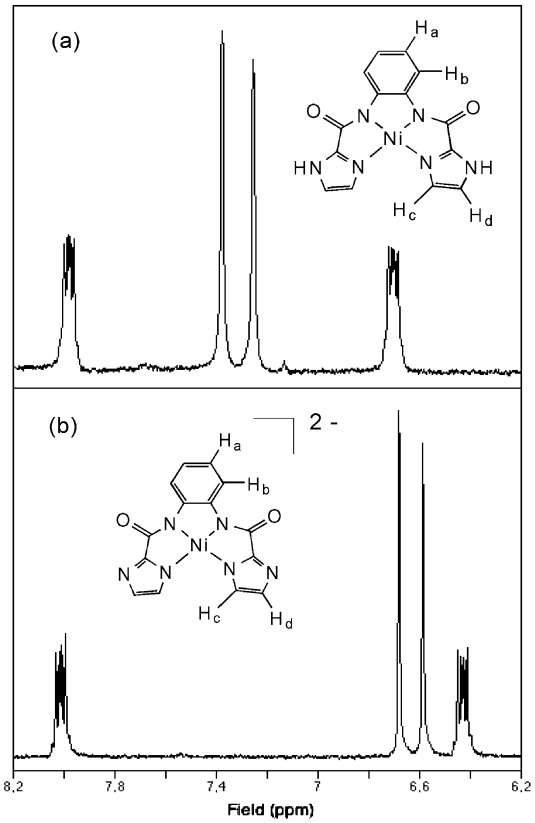


Figure 3. ^1H NMR spectra of $[NiLH_2]$ (a) and $[NiL]^{2-}$ (b) in DMSO-d^6 (250 MHz).

2. Summary and conclusions

We have synthesised a novel tetradentate ligand bearing two amido groups and two imidazole rings. Preliminary results on the relationship between the electronic and the electrochemical properties of the corresponding metal complexes and the protonic states of the ligand are highly stimulating. We are pursuing the investigation of the oxidised species of the nickel(II) complexes and extend the synthesis of metal complexes to other first transition metal ions.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.03.077.

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